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Translocation t(1;19)(q23;p13) in Adult Acute Lymphoblastic Leukemia – A Distinct Subtype with Favorable Prognosis

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Abstract

The recurring translocation t(1;19) (q23;p13) with *TCF3-PBX1* rearrangements are uncommon in adult acute lymphoblastic leukemia (ALL), and their prognostic impact remains to be described in the era of modern chemotherapies. We investigated 427 adult patients with newly diagnosed pre-B ALL, 16 (4%) had t(1;19)(q23;p13) at diagnosis. All 16 patients achieved complete remission after induction with intensive chemotherapy, and with a median of 7-year follow-up, 2 relapsed. The 5-year cumulative incidence of relapse and overall survival rates were 14% and 82%, respectively. Our analysis showed that adult patients with t(1;19)(q23;p13) positive ALL had favorable prognosis with intensive chemotherapy regimens.

Keywords

t(1;19); TCF3-PBX1; ALL; outcome; prognosis

Introduction

The recurring chromosomal t(1;19) translocation is a well-described acute lymphoblastic leukemia (ALL) specific cytogenetic abnormality¹. This translocation may occur in a balanced t(1;19) (q23;p13) or unbalanced +der(19)t(1;19) (q23;p13) form, in which the derivative chromosome 19 is only present². The translocation leads to a fusion of the transcription factor 3 gene (*TCF3*, previously *E2A*) at 19p13 with the pre-B cell leukemia homeobox 1 gene (*PBX1*) at 1q23 to form *TCF3-PBX1*³. *TCF3* encodes transcription

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Conflict of Interest:

Authors have no relevant conflict of interest to declare

factors E12 and E47, which are required for regulation of B-cell development and normal lymphopoiesis⁴. The abnormal protein product of the gene fusion alters cell differentiation and results in leukemia^{5,6}. Upon initial identification of the t(1;19) in mid 1980s, patients with this cytogenetic abnormality were associated with poor prognosis¹, with a high incidence of central nervous system (CNS) relapses⁷⁻⁹. However, the use of intensive ALL therapies in modern protocols has improved the outcomes, specifically in children¹⁰. Due to the rarity of t(1;19) in adult ALL, we have limited knowledge of its prognostic significance in this patient population. Previous reports were limited due to the small cohort size and the heterogeneity of treatment modalities¹¹. Herein, we update our experience with a larger cohort of patients with t(1;19)-positive ALL who were treated with either hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyperCVAD)¹² or Augmented Berlin-Frankfurt-Münster Therapy (Augmented-BFM)¹³ regimens; we aim to identify the prognostic significance of t(1;19) on outcomes and compare it with other common cytogenetic groups in ALL.

Patients and Methods

We performed a retrospective review of 427 adult patients with newly diagnosed Philadelphia chromosome-negative pre-B-ALL treated between 1992 and 2017 at The University of Texas MD Anderson Cancer Center (MDACC). After the year 2000, anti-CD20 monoclonal antibody therapy was added to the regimens for patients with CD20 positive disease (if CD20 expression >20%). The augmented-BFM regimen was administered in patients younger than 40 years old. The details of these chemotherapy regimens were previously published^{14,15}. This study was approved by the institutional review board of MDACC in accordance with the Declaration of Helsinki.

Cytogenetic studies were performed on bone marrow samples obtained prior to induction chemotherapy. International System for Cytogenetic Nomenclature criteria was used to interpret karyotype¹⁶. Forty-five patients with no available karyotype data were excluded from analysis. In total, 382 patients were grouped according to the Medical Research Council United Kingdom Acute Lymphoblastic Leukemia (UKALL)XII/ Eastern Cooperative Group (ECOG) karyotype categories¹⁷: (1) 16 patients with t(1;19) (q23;p13); (2) 25 patients with t(4;11) (q21;q23); (3) 21 patients with complex karyotype (5 or more chromosomal abnormality); (4) 30 patients with hypodiploidy/neartriploidy (Ho-Tr) (5) 31 patients with high hyperdiploidy (6) 138 patients with normal karyotype (7) 121 patients with near diploidy. Three cases with constitutional karyotype findings (trisomy 21) were evaluated in near diploidy group. Florescence In Situ Hybridization (FISH) for TCF3-PBX1 was standard of care at our institution since 2010; five patients were confirmed with FISH.

The details regarding response assessment, definitions of overall survival (OS), and methodology of flow cytometry were previously reported^{18,19}. The relationship between karyotype groups and categorical variables were analyzed using the Fisher exact test, and the Kruskal-Wallis test was used to analyze continuous variables. Survival estimates were computed by Kaplan-Meier approach and survival comparisons performed using the log rank test. Relapse and non-relapse mortality were shown as cumulative incidence curve to adjust analysis for competing risks. The Gray test was used to calculate cumulative

incidence of relapse. Multivariate Cox proportional hazards models were used to identify any association with clinical variables and OS. Computations were performed with SPSS (version 23) and SAS University Edition statistical programs.

Results

Clinical characteristics of the 16 patients with t(1;19) were summarized and compared to other cytogenetic subgroups (Table 1). Patients with t(1;19) were younger at diagnosis than patients with other cytogenetic abnormalities. All patients with t(1;19) achieved CR after induction with HyperCVAD (n=14) or Augmented BFM (n=2). Eleven of the 12 patients (92%) assessed for MRD status achieved MRD negative CR at approximately 4 weeks post induction (Supplementary Table 1). In total, two patients (12%) relapsed after 15 and 22 months of remission; (1 systemic and 1 CNS only). With a median follow-up of 7 years, two patients (12%) died; 1 from disease progression at 16 and 1 in CR at 10 months. Three patients (18%) received allogeneic stem cell transplantation (allo-SCT) in first CR (CR1); all were alive and in remission at last follow-up, 2 of them in CR1 and one in CR2.

Among all cytogenetic groups, the 5-year cumulative incidence of relapse probability was the lowest, 14%, for patients in t(1;19) group (p=0.001); it was 26%, 36%, 38%, 43%, 63%, and 68% for high-hyperdiploid, Ho-Tr, diploid, near diploid, complex and MLL, respectively (Figure 1A). Patients with t(1;19) had a significantly superior OS (5-year OS of 82%) when compared with other groups (p=0.001) (Figure 1B).

Among all cytogenetic categories, t(1;19) patients were the youngest, median age of 28 years (table 1). To understand the impact of age, cytogenetics and other clinical variables on survival, we performed a multivariate analysis. While older age, higher WBC count, low albumin, ECOG 2, and t(4;11) were associated with inferior OS, t(1;19) had no impact (Supplementary table 2).

Discussion

In contrast to previous suggestions^{20–24}, we have shown that adult patients with t(1;19) positive ALL do not appear to have inferior outcomes than other cytogenetic subgroups. Data suggesting that t(1;19) confers poor prognosis in ALL were initially published in pediatric literature¹. In a study of 285 children with newly diagnosed pre-B ALL treated by the Pediatric Oncology Group, 29 patients (10%) were identified to have with t(1;19); the 2-year EFS rate was 40% as opposed to 90% in those with other cytogenetic abnormalities²⁵. However, with the development of intensive treatment protocols, the outcome of pediatric patients with t(1;19) has remarkably improved. In an Austrian study, 859 children with ALL were treated on ALL-BFM clinical trials; 31 patients (4%) with t(1;19)²⁶. Using intensive chemotherapy protocol, investigators reported a 5-year EFS rate of 90% in their patients.

Adult patients with t(1;19) positive ALL tend to be younger. However, the favorable outcomes demonstrated in pediatric patients were not reproduced in adult patients with t(1;19) ALL. In German Multicenter Therapy Study Group for Adult Acute Lymphoblastic Leukemia, the 5-year OS rate was reported as 51% for the 23 patients (median age 27) with t(1;19); 6 (26%) received allo-SCT in CR1²⁷. In the LALA-94 French trial, of the 24 ALL

patients (median age 31) with t(1;19), the 5-year OS was 31% (9 (38%) received allo-SCT in CR1)²⁸ These results are in contrast with our study where the minority of the patients (18%) received allo-SCT as consolidation. Perhaps, the favorable survival obtained in our series could be due to modern intensive regimens, which includes high dose cytarabine and methotrexate, prolonged maintenance therapy, in addition to the CNS directed treatment. Allo-SCT is reserved for patients with high-risk cytogenetic abnormalities, including t(4;11) *KMT2A*-rearrangement, complex karyotype (defined as ≥ 5 unrelated clonal abnormalities), and Ho-Tr.

In a recently published study, Lafage-Pochitaloff et al. reported outcomes in 28 adult patients with t(1;19) positive B-ALL treated with relatively homogenous pediatric-inspired regimens in intensified Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL)-2003/2005 trials.²⁹ The 5-year cumulative incidence of relapse rate was reported as 29% in t(1;19) positive patients compared with 23% in patients with no cytogenetic abnormality (n=122); 5-year OS rates 57% versus 63%, respectively. These findings support our findings suggesting that B-ALL patients with t(1;19) do not have an inferior prognosis when treated with modern intensive chemotherapy regimens.

We note several limitations to our study. Detection of t(1;19) relied mainly on karyotype because FISH analysis for TCF3-PBX1 became standard of care after 2010. Besides, due to the rarity of t(1;19) in B-ALL, our cohort size was small with 16 patients. We also performed a multivariate analysis including age, t(1;19), and other clinical variables, and found that t(1;19) was not independently associated with superior OS (Supplementary Table 2). Translocation (1;19) is commonly seen in younger patients^{27,29}; the median age was 28 years in this study cohort, which may have been partly responsible for the superior OS demonstrated in patients with t(1;19) (Figure 1A).

Primary chromosomal alterations still remain as strong prognostic markers in adult ALL³⁰. We conclude that adult patients with t(1;19)(q23;p13) positive ALL have a favorable outcome when treated with modern intensive regimens such as Hyper-CVAD or the augmented BFM.

Supplementary Material

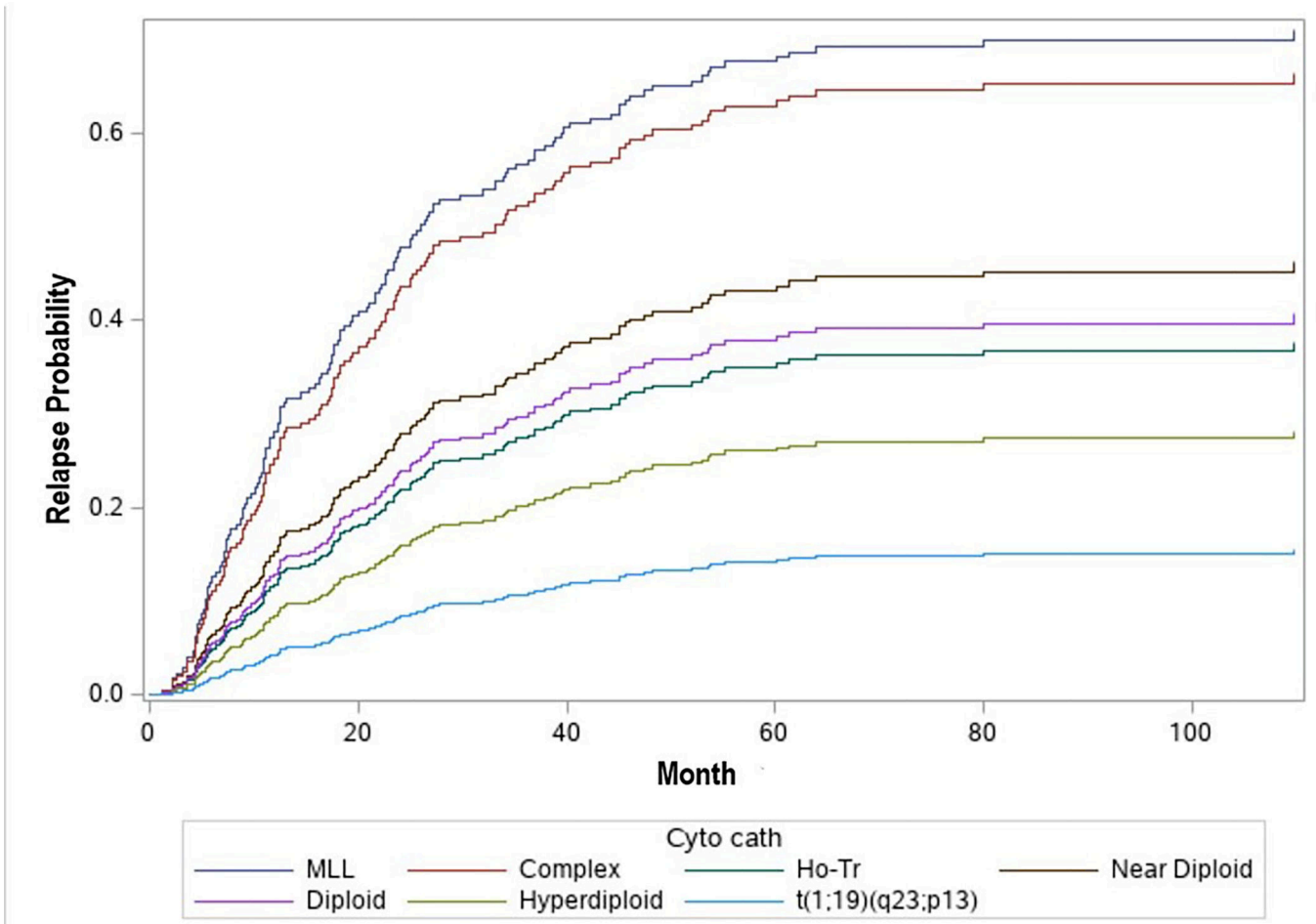
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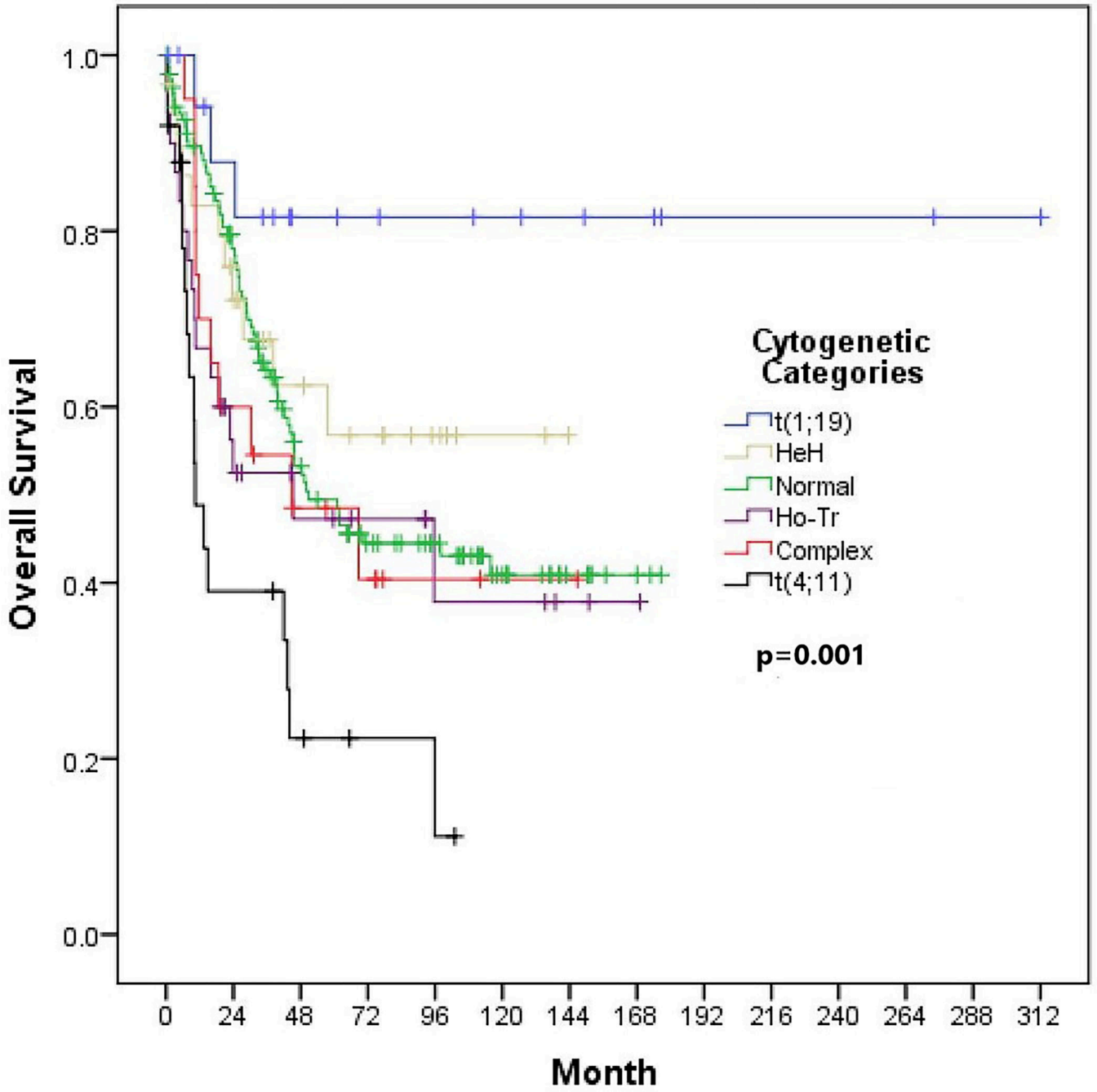


Figure 1. Cumulative incidence of relapse (A) and overall survival (B) by cytotenetic group. Heh: high hyperdiploidy; Normal: normal karyotype; Ho-Tr: hypodiploidy/neartriploidy; Complex: complex karyotype.

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Table 1.
Baseline clinical characteristics, treatments and responses by karyotype subgroups

Characteristics	All (n=382)	t(1;19) (n=16)	Diploid (n=138)	Near Diploid (121)	Ho-Tr (n=30)	HeH (n=31)	t(4;11) (n=25)	Complex (n=21)	p
Age	38 [15-83]	28 [17-41]	38 [16-84]	39 [15-83]	55 [17-78]	30 [19-73]	48 [22-75]	36 [15-70]	<0.01
Gender (male)	203 (53)	13 (72)	82 (59)	58 (48)	15 (50)	16 (52)	6 (25)	13 (62)	0.02
WBC count, 10 ⁹ /L	4 [0.4-602]	14 [1.5-170]	3.5 [0.4-158]	4.5 [0.4-602]	4.2 [1-602]	2 [0.6-22]	9 [0.5-316]	4 [0.6-30]	<0.01
Hemoglobin, g/L	9 [3.5-15]	9 [3.6-12]	8.8 [3.5-15]	9 [4-14]	9 [4-13]	9.2 [5-14]	9.2 [7.4-11]	9 [5-12]	0.58
Platelets, 10 ⁹ /L	45 [0-626]	32 [11-150]	65 [4-626]	36 [0-383]	31 [3-242]	49 [11-171]	37 [6-100]	32 [2-513]	<0.01
BM blasts, %	87 [0-100]	91 [43-98]	83 [0-99]	88 [1-100]	79 [31-98]	85 [20-98]	90 [28-97]	87 [7-98]	<0.01
Albumin	3.5 [1.9-5.2]	3.4 [2.7-4.6]	3.5 [2-5]	3.4 [2-5.1]	3.5 [2.5-5]	3.4 [2.4-5.2]	3.4 [2-4.5]	3.5 [2-5]	0.67
T. Bilirubin	0.5 [0.1-1.1]	0.5 [0.2-1]	0.5 [0.1-8.7]	0.6 [0.2-1.1]	0.5 [0.2-1.6]	0.5 [0.2-1.3]	0.4 [0.2-1.7]	0.5 [0.1-5]	0.6
Creatinine	0.8 [0.3-3.2]	0.8 [0.5-1.2]	0.8 [0.3-3.2]	0.8 [0.4-2.3]	0.8 [0.5-2.3]	0.8 [0.4-1.2]	0.7 [0.5-1.4]	0.8 [0.4-1.5]	0.53
Treatment									
HyperCVAD	297 (78)	14 (87)	115 (83)	83 (69)	28 (93)	25 (81)	22 (87)	11 (52)	<0.01
Augmented-BFM	85 (22)	2 (13)	23 (17)	38 (31)	2 (7)	6 (19)	2 (13)	10 (48)	
Morphologic Response									
CR/CRi	361 (94)	16 (100)	131 (95)	112 (93)	28 (93)	30 (97)	23 (92)	21 (100)	0.33
NR	11 (3)	0	6 (4)	4 (3)	0	0	0	0	
Early Death	10 (3)	0	1 (1)	5 (4)	2 (7)	1 (3)	2 (8)	0	

Ho-Tr, hypodiploidy-near triploidy; HeH, high hyperdiploidy; Complex, complex karyotype; WBC, white blood cell; BM, bone marrow; T, total; CR, complete response; CRi, CR with incomplete count recovery; NR, no response 124 patients with miscellaneous karyotype were not shown in this table